July 16, 1948.

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Dear Mike,

Your letter was most interesting. Good luck. If maltose is phosphorolysed, certain questions must come up, about which you must already have been thinking. Is glucose accumulated during the utilisation of maltose? A rather crude expt. I did here suggested that it was not. Then are we dealing with a "transglucosidase"? What happens to the 4-substituted "aglycon" glucose, unless perhaps there is a preliminary phosphorylation to maltose-1-phosphate, which is subsequently phosphorolysed to 2 moles of glucose-1-phosphate.

I am sending you 'stat' the following cultures:

K-12, the granddaddy wild type. (No nutritional mutations)

Y-10, the triple mutant requiring threonine, leucine, thiamin. ($T-L-B_1-$)

W-108, the so-called Lac_3- from Y-10, unable to split lactose or maltose or to ferment glucose. You already know the procedure by which this was obtained.

You already have W-327, the Mal+Glu-. This was obtained from W-108 by inoculating heavy suspensions into synthetic medium containing T,L,B_1 and maltose as the sole carbon source. In addition to reversions of Lac_3- to Lac_3+, this procedure also selected for Mal+ types which on further test proved to be glucose-. When crossed with wild type (B-M-;biotin-methionineless) Mal- prototrophs were found as well as the two parental fermentation types. This proves that W-327 is not a different allele of Lac_3-, but that some other gene has mutated which to use a horrible terminology, partially "suppresses" the effects of Lac_3-. The genetic formula for this type is, therefore, T-L-B-Lac$_3$-S$_{L3M}$+. It should accumulate an unknown different biochemical pathway from that which was blocked by the mutation Lac_3-. Also, the gene at the S_{L3M} locus may have had entirely different functions which we do not now know. I am going to try to get at that problem by selecting for Mal- mutations in the W- stock, and see what happens. I also have to find out the effect of combing S_{L3M}+

Lac_3- to distinguish it from other lac-mutations involving different genes, I.... S. It was obtained on Lactose EMB

with other maltose-negative mutants, but the genetics of that situation will be exceedingly complicated. If I may venture the suggestion, I think it will be exceedingly important to compare the mode of maltose utilization in Y-10 (Lac_3^+) and in Lac_3-S..+

I have tried to select out comparable stocks for trehalose, but all that I got were reversions of Lac_3, and a very slow glucose+/trehalose+, others? I have done very little with melibiose, since the wild type seems to ferment itsomewhat weakly, and I could not get so sharp differentiations on the indicator media.

As to lactose, it is a simple matter to extract a galactosidase from lactose-adapte cultures of K-12, and I am just getting down to work on it with the help of nitrophenyl galactoside as a chromogenic substrate. I can send you a culture, W-252 which is lactose+ glucose negative, obtained from W-103, and of the constitution Lac_3-S_{L31}+ . However, W-103 is still fairly strongly galactose+. I have thought that probably glucose would be accumulated during lactose utilization by this strain, but it is also possible that the S... mutation has opened up a new phosph. pathway. I will also send you W-254 which is Gal- (obtained as such, and no genetic shenanigans about it) and Lac+. This definitely accumulates monose (presumably galactose) during lactose utilization, as tested directly, and as would be inferred from the very active lactose hydrolase that can be extracted from it.

I have been trying, so far unsuccessfully to find simple glucose-negative mutants which would behave analogously to W-254 and accumulate glucose, still being Lac+. If the combination Glu- Gal- turned out to be Lac+, while each of the pairs Glu-Gal+ and Glu+Gal- were Lac+ and accumulated monose, it would be strong corroborative evidence that the sole pathway of lactolysis in the wild type was hydrolytic. But to do this I need the Glu- type, and haven't got it yet. But we're going strong with some new methods for detecting mutants (using tetrazolium) and hope to have them, soon!

I am delighted at your suggestion that you come here for part of 1949-50. We're somewhat crowded for space in the Genetics Building, but I'm sure that something can be worked out which will be very beneficial to both of us.

With best regards,

Yours sincerely,

Joshua Lederberg.